CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 089628

Trade Name :LEUCOVORIN CALCIUM FOR INJECTION

Generic Name: Leucovorin Calcium for Injection

Sponsor : Pharmachemie B.V.

Approval Date: April 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 089628

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 089628

APPROVAL LETTER

ANDAs 89-628 (50 mg (base)/vial)
89-915 (100 mg (base)/vial)

APR 17 1997

Pharmachemie B.V.
Attention: Hellen de Kloet (Agent)
323 Davis Street
Northborough, Massachusetts 01532

Dear Madam:

This is in reference to your abbreviated new drug applications dated January 13, 1987 (89-628) and January 12, 1988 (89-915), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leucovorin Calcium for Injection.

Reference is also made to your amendments dated October 28, 1996, and January 3, March 17, and April 11, 1997.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Leucovorin Calcium for Injection, 50 mg and 100 mg (base) per vial, to be bioequivalent and, therefore therapeutically equivalent, to the listed drug, Leucovorin Calcium for Injection, 50 mg and 100 mg (base) per vial, respectively, of Immunex Corp.

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

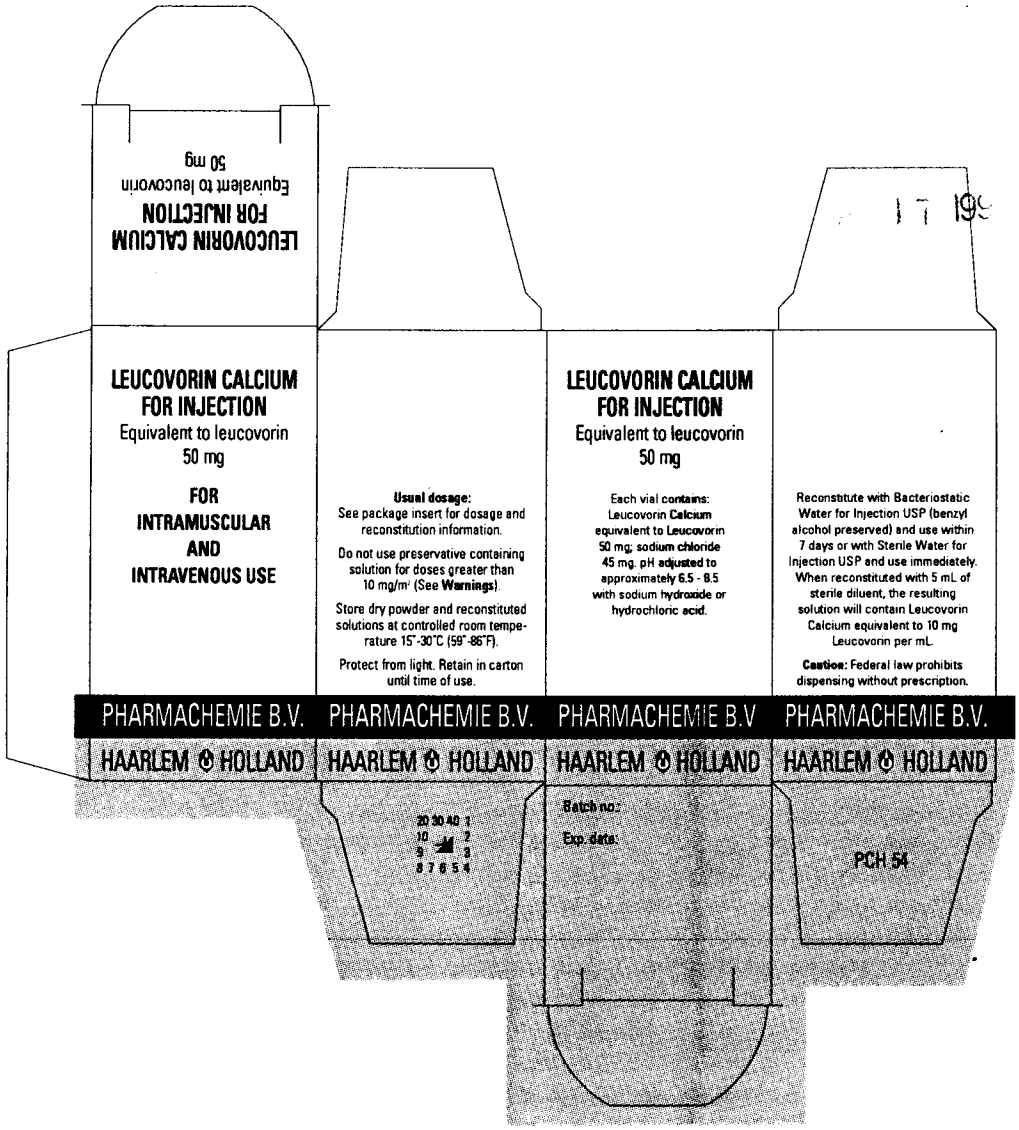
Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 089628

FINAL PRINTED LABELING


LEUCOVORIN CALCIUM
FOR INJECTION
Equivalent to leucovorin
50 mg
LEUCOVORIN CALCIUM
FOR INJECTION
Equivalent to leucovorin
50 mg
FOR
INTRAMUSCULAR
AND
INTRAVENOUS USE
Usual dosage:
See package insert for dosage and reconstitution information.
Do not use preservative containing solution for doses greater than 10 mg/m² (See Warnings).
Store dry powder and reconstituted solutions at controlled room temperature 15°-30°C (59°-86°F).
Protect from light. Retain in carton until time of use.
LEUCOVORIN CALCIUM
FOR INJECTION
Equivalent to leucovorin
50 mg
Each vial contains:
Leucovorin Calcium equivalent to Leucovorin 50 mg; sodium chloride 45 mg. pH adjusted to approximately 6.5 - 8.5 with sodium hydroxide or hydrochloric acid.
Reconstitute with Bacteriostatic Water for Injection USP (benzyl alcohol preserved) and use within 7 days or with Sterile Water for Injection USP and use immediately. When reconstituted with 5 mL of sterile diluent, the resulting solution will contain Leucovorin Calcium equivalent to 10 mg Leucovorin per mL.
Caution: Federal law prohibits dispensing without prescription.
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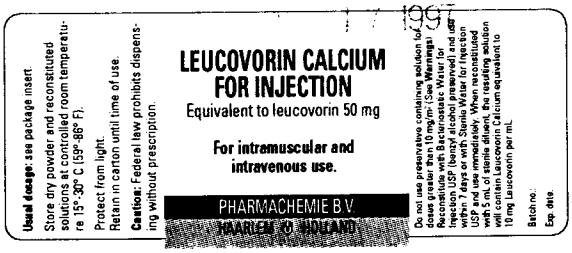
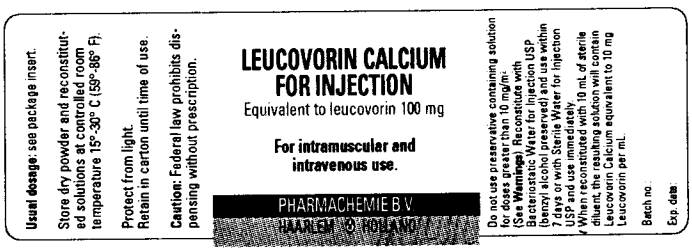
HAARLEM HOLLAND
PHARMACHEMIE B.V.
HAARLEM HOLLAND
PHARMACHEMIE B.V.
HAARLEM HOLLAND
Batch no.:
Exp. data:
PCH 54

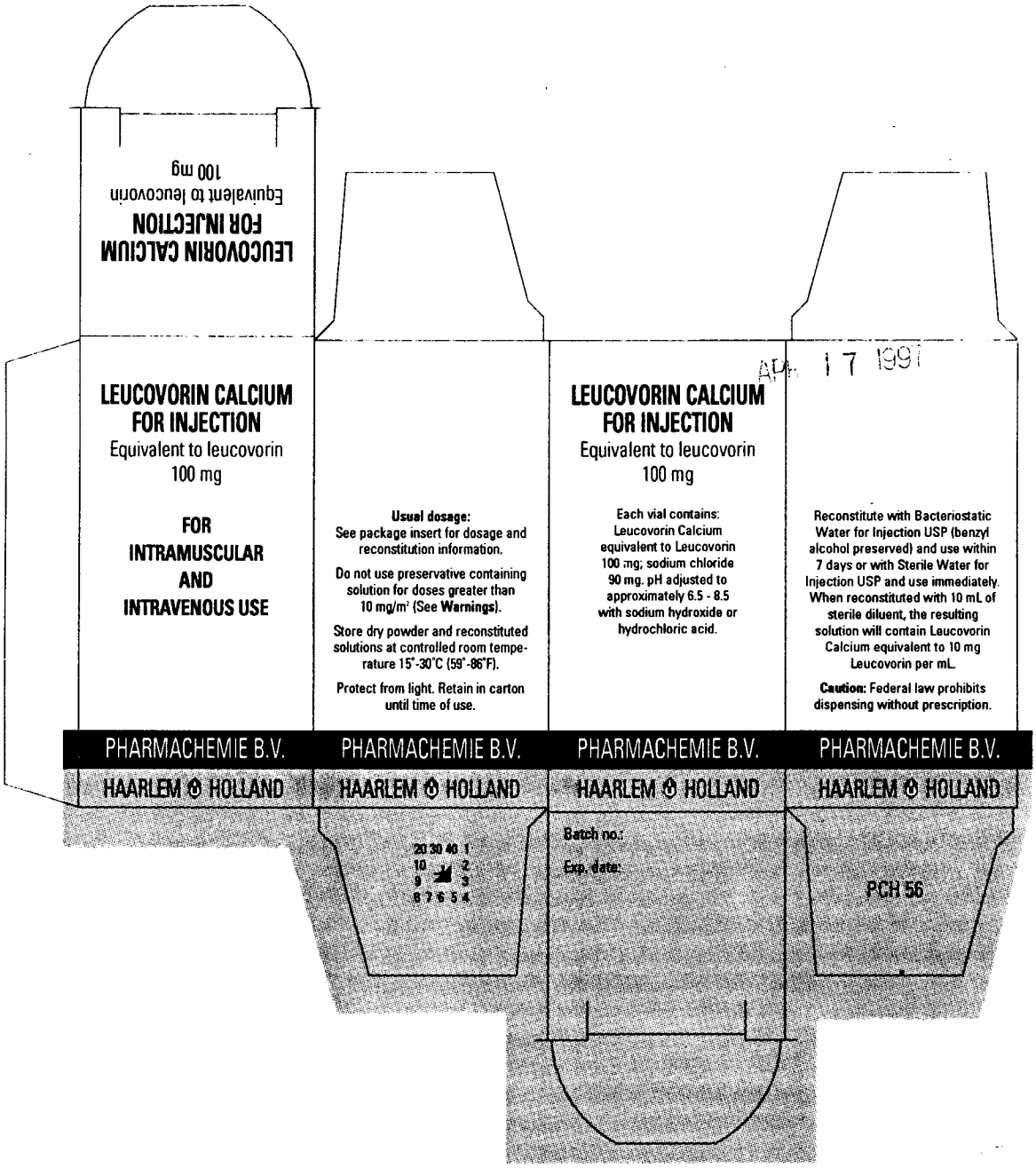
LEUCOVORIN CALCIUM
50mg
30*74mm / 2mm hoekafronding



LEUCOVORIN CALCIUM
100mg
30*90mm / 2mm hoekafronding

APR 17 1997




LEUCOVORIN CALCIUM
FOR INJECTION
Equivalent to leucovorin
100 mg
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FOR INJECTION
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INTRAMUSCULAR
AND
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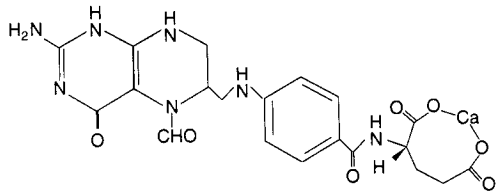
Usual dosage:
See package insert for dosage and reconstitution information.
Do not use preservative containing solution for doses greater than 10 mg/m² (See Warnings).
Store dry powder and reconstituted solutions at controlled room temperature 15°-30°C (59°-86°F).
Protect from light. Retain in carton until time of use.
Each vial contains:
Leucovorin Calcium equivalent to Leucovorin 100 mg; sodium chloride 90 mg. pH adjusted to approximately 6.5 - 8.5 with sodium hydroxide or hydrochloric acid.
Reconstitute with Bacteriostatic Water for Injection USP (benzyl alcohol preserved) and use within 7 days or with Sterile Water for Injection USP and use immediately. When reconstituted with 10 mL of sterile diluent, the resulting solution will contain Leucovorin Calcium equivalent to 10 mg Leucovorin per mL.
Caution: Federal law prohibits dispensing without prescription.
PHARMACHEMIE B.V.
HAARLEM HOLLAND
PHARMACHEMIE B.V.
HAARLEM HOLLAND
20 30 40 1
10 2
9 3
8 7 6 5 4
PHARMACHEMIE B.V.
HAARLEM HOLLAND
Batch no.:
Exp. date:
PHARMACHEMIE B.V.
HAARLEM HOLLAND
PCH 56

LEUCOVORIN CALCIUM FOR INJECTION

DESCRIPTION

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolic acid, this compound has the chemical designation of Calcium N-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)-methyl]amino]benzoyl]-L-Glutamic acid (1:1). Leucovorin calcium has a molecular weight of 511.51 and the following structural formula:



$C_{20}H_{21}CaN_7O_7$

Leucovorin Calcium for Injection is a sterile product indicated for intravenous or intramuscular administration and is supplied in 50 mg and 100 mg vials. Each vial contains the following inactive ingredients: sodium chloride 45 mg/vial for the 50 mg vial and 90 mg/vial for the 100 mg vial, sodium hydroxide and/or hydrochloric acid to adjust the pH to 6.5-8.5 during manufacture. The 50 and 100 mg vials are preservative free.

There is 0.004 mEq of calcium per mg of leucovorin.

CLINICAL PHARMACOLOGY

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-*l*-isomer, known as Citrovorum factor, or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. *l*-Leucovorin (*l*-5-formyltetrahydrofolate) is rapidly metabolized (via 5,10-methenyltetrahydrofolate then 5,10-methylenetetrahydrofolate) to *l*,5-methyltetrahydrofolate. *l*,5-Methyltetrahydrofolate can in turn be metabolized via other pathways

PHARMACHEMIE B.V.
Postbus 552
2003 RN Haarlem

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back to 5,10-methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors $FADH_2$ and NADPH.

Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after intravenous and intramuscular administration of a 25 mg dose of leucovorin were studied in male volunteers. After intravenous administration, serum total reduced folates (as measured by *Lactobacillus casei* assay) reached a mean peak of 1259 ng/mL (range 897-1625). The mean time to peak was 10 minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by *Streptococcus faecalis* assay) which rose to 1206 ng/mL at 10 minutes. A sharp drop in parent compound followed and coincided with the appearance of the active metabolite 5-methyl-THF which became the predominant circulating form of the drug.

The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The area under the concentration versus time curves (AUCs) for *l*-leucovorin, *d*-leucovorin and 5-methyltetrahydrofolate were 28.4 ± 3.5, 956 ± 97 and 129 ± 12 (mg.min/L ± S.E.). When a higher dose of *d,l*-leucovorin (200 mg/m²) was used, similar results were obtained. The *d*-isomer persisted in plasma at concentrations greatly exceeding those of the *l*-isomer.

After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/mL (range 240 to 725) and occurred at 52 minutes. Similar to IV administration, the initial sharp rise was due to the parent compound. The mean peak of 5-formyl-THF was 360 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference of statistical significance between IM and IV administration in the AUC for total reduced folates, 5-formyl-THF, or 5-methyl-THF.

INDICATIONS AND USAGE

Leucovorin calcium rescue is indicated after high dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.

CONTRAINDICATIONS

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B_{12}. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosages of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g., methotrexate) and leucovorin rescue increases, leucovorin's effectiveness in counteracting toxicity decreases. Do not administer leucovorin intrathecally.

Monitoring the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Because of the benzyl alcohol contained in certain diluents used for reconstituting Leucovorin Calcium for Injection, when doses greater than 10 mg/m² are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP and used immediately (see DOSAGE AND ADMINISTRATION).

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute. (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of the 5-fluorouracil must be lower than usually administered. Although the toxicities observed in patients treated with the combination of leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities

(particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in patients treated with the combination.

Therapy with leucovorin and 5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In a study utilizing higher weekly doses of 5-FU and leucovorin, elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity[1].

PRECAUTIONS

General

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on non-hematologic toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Drug Interactions

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of 5-fluorouracil (see WARNINGS).

Pregnancy: Teratogenic Effects:
"Pregnancy Category C". Adequate animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when leucovorin is administered to a nursing mother.

Pediatric Use:
See Drug Interactions.

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin *per se*.

OVERDOSAGE

Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION

Leucovorin Rescue After High-Dose Methotrexate Therapy:

The recommendations for leucovorin rescue are based on a methotrexate dose of 12 to 15 grams/m² administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information)[2].

Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.
Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5×10^{-8} M (0.05 micromolar). The leucovorin dose should be adjusted or leucovorin rescue extended based on the following guidelines:

GUIDELINES FOR LEUCOVORIN DOSAGE AND ADMINISTRATION
DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR: a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Impaired Methotrexate Elimination or Inadvertent Overdosage:

Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is a delayed excretion (See WARNINGS). Leucovorin 10 mg/m^2 should be administered IV, IM or PO every 6 hours until the serum methotrexate level is less than 10^{-6} M. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5×10^{-6} M or the 48 hour level is greater than 9×10^{-7} M, the dose of leucovorin should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M.

Hydration (3 L/d) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Megaloblastic Anemia Due to Folic Acid Deficiency:

Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Preparation:

Each 50 and 100 mg vial of Leucovorin Calcium for Injection when reconstituted with 5 and 10 mL, respectively, of sterile diluent yields a leucovorin concentration of 10 mg per mL. Leucovorin Calcium for Injection contains no preservative. Reconstitute with Bacteriostatic Water for Injection USP, which contains benzyl alcohol, or with Sterile Water for Injection USP. When reconstituted with Bacteriostatic Water for Injection USP the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection USP, it must be used immediately (see WARNINGS).

Because of the benzyl alcohol contained in Bacteriostatic Water for Injection USP, when doses greater than 10 mg/m^2 are administered, Leucovorin Calcium for injection should be reconstituted with Sterile Water for Injection USP, and used immediately.

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL; or 8 mL of a 20 mg/mL solution per minute).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Leucovorin Calcium for Injection, vials of 50 mg or 100 mg leucovorin lyophilized powder for injection (NDC 53989-110-50), packed in individual cartons. Unopened vials of dry powder of Leucovorin Calcium for Injection, as well as reconstituted solution should be stored at controlled room temperature, 15°-30°C (59°-86°F), protected from light.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

REFERENCES

1. Grem, JL, Shoemaker, DD, Petrelli, NJ, Douglas, HO, "Severe and Fatal Toxic Effects Observed in Treatment with High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma", *Cancer Treat Rep* 1987; 71:1122.
2. Link, MP, Goorin, AH, Miser, AW, *et al.* "The Effect of Adjuvant Chemotherapy on Relapse-Free Survival in Patients with Osteosarcoma of the Extremity." *N Engl J Med* 1986; 314:1600-1606.

MANUFACTURER

Pharmachemie B.V.
Haarlem
The Netherlands.

DISTRIBUTOR

Pharmachemie USA, Inc
Oradell, NJ 07649.

DATE

January 1997.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 089628

CHEMISTRY REVIEW(S)

Chem Closed

1/2. CHEMISTRY REVIEW NO.9: ANDA #89-628

CHEMISTRY REVIEW NO. 5: ANDA #89-915

3. NAME AND ADDRESS OF APPLICANT

Applicant: Pharmachemie BV
Swensweg 5
Haarlem, The Netherlands

U.S. Agent: Pharmachemie U.S.A., Inc.
P.O. Box 145
Oradell, New Jersey 07649

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Leucovorin Calcium

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES: ANDA 89-628:

January 13, 1987 - original submission
February 20, 1987 -Bio waiver granted
June 12, 1987 - chem review #1, NAL
November 2, 1987 - amendment responding to 6/12/87 NAL
January 21, 1988 - NAL for chem review #2
March 18, 1988 - amendment responding to 1/21/88 NAL
May 9, 1988 - NAL for chem review #3 dated 5/2/88
August 25, 1988 - amendment responding to 5/9/88 NAL
September 30, 1988 - NAL for chem review #4 dated 9/27/88
December 12, 1988 - amendment responding to 9/30/88 NAL
March 21, 1989 - amendment (labeling concerns)
March 24, 1989 - amendment (request 24 month expiry date)
June 12, 1989 - amendment (withdrawing 3/24/89 request)
August 14, 1989 - NAL for chem review #5 dated 8/3/89
August 31, 1989 - amendment responding to 8/14/89 NAL
July 17, 1990 - NAL for chem review #6 dated 5/3/90
February 1, 1991 - Identifying US agent
February 1, 1991 - Notification of intention to respond to 7/17/90 NAL
February 6, 1991 - ONC (new facility)
September 24, 1992 - ONC (Notification of intention to respond to NAL)
February 14, 1994 - ONC (ANDA is still active)
June 6, 1994 - ONC (ANDA is still active)

November 4, 1994 - ONC (Notification of intention to respond to NAL)
December 9, 1994 - amendment responding to NAL dated 7/17/90 - notification of a new manufacturing site
May 16, 1995 - NAL for chem review #7
May 13, 1996 - amendment responding to NAL of 5/16/95
*October 28, 1996 - amendment responding to NAL of 8/1/96

AMENDMENTS AND OTHER DATES: ANDA 89-915:

January 12, 1988 - original submission
March 2, 1988 - ONC (revised labeling certification statement)
March 2, 1988 - ONC (replacement pages)
March 7, 1988 -Bio waiver granted
April 29, 1988 - chem review #1, NAL
September 22, 1988 - amendment responding to 4/29/88 NAL
March 1, 1989 - NAL re: 9/22/88 amendment
June 19, 1989 - amendment responding to 3/1/89 NAL
March 13, 1990 - NAL for review #2
April 25, 1990 - NAL regarding micro review #1 dated 3/9/90
February 1, 1991 - Identifying US agent
February 1, 1991 - Notification of intention to respond to 4/25/90 NAL
February 6, 1991 - ONC (new facility)
September 24, 1992 - ONC (Notification of intention to respond to NAL)
June 6, 1994 - ONC (ANDA is still active)
November 4, 1994 - ONC (Notification of intention to respond to NAL)
December 9, 1994 - amendment responding to letter dated 4/25/90 (micro issues); notification of a new manufacturing site
May 16, 1995 - NAL for chem review #3
May 13, 1996 - amendment responding to NAL of 5/16/95
*October 28, 1996 - amendment responding to NAL of 8/1/96

10. PHARMACOLOGICAL CATEGORY

Antidote to folic acid antagonists
Antianemic (folate deficiency)

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Lyophilized Powder

14. POTENCY

50 mg/vial (ANDA 89-628)
100 mg/vial (ANDA 89-915)

15. CHEMICAL NAME AND STRUCTURE

ANDA 89-628:
ANDA 89-915:

16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

18. CONCLUSIONS AND RECOMMENDATIONS

A. CHEMISTRY

Issues are closed.

B. LABELING

Review of October 28, 1996 amendments - pending.

C. EERs

Updated EERs dated 4/26/95 - pending.

19. REVIEWER: DATE COMPLETED:

11/7/96

Shirley S. Brown November 7, 1996

cc: ANDAs #89-628 & #89-915
DUP File
Division File
Field Copy

Endorsements: 11/7/96

HFD-625/SBrown
HFD-625/MSmela
X:\new\firmsnz\pharmach\ltrs&rev\89628apl.915
F/T by:

Labeling satisfactory with 1/3 and 3/7/97 amendments.
EER acceptable on 1/29/97

3/26/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 089628

BIOEQUIVALENCE REVIEW(S)

NDA 89-628

Pharmachemie U.S.A., Inc.
Attention: J. David Hayden
P.O. Box 145
Cradell, NJ 07649

FEB 20 1987

Dear Sir:

Reference is made to your request for waiver of in-vivo bioavailability requirements you submitted on January 13, 1987 for Leucovorin Calcium Injection (Lyophilized Powder) 50 mg.

Your request has been reviewed by our Division of Bioequivalence and they have the following comments:

"1. The Division of Bioequivalence agrees that the information submitted by Pharmachemie USA, Inc. demonstrates that its leucovorin calcium lyophilized powder for injection, 50 mg per vial, falls under 21 CFR 320.22 (c)(2) of the Bioequivalence Regulations. The waiver of an in-vivo bioequivalence study for leucovorin calcium lyophilized powder for injection, 50 mg per vial, is granted for the test product. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Lederle's leucovorin calcium lyophilized powder for injection, 50 mg per vial."

Sincerely yours,

Marvin Seife 2/20/87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: HFN-230
Brancato
MSeife/JSturm/jt/2-17-87
BIO 0663b

2/11/87

Leucovorin Calcium
Lyophilized Powder
50 mg vial
ANDA #89-628
Reviewer: J.F. Kinsel
Wang #9382e

Pharmachemie USA, Inc.
Oradell, N.J.
Submission Date:
January 13, 1987

REVIEW OF A REQUEST FOR WAIVER OF IN-VIVO BIOAVAILABILITY REQUIREMENTS

The firm has requested a waiver of an in-vivo bioavailability study for its leucovorin calcium lyophilized powder for injection, 50 mg per vial, under 21 CFR 320.22 (c)(2). The waiver request is predicated on both formulations being identical with respect to active and inactive ingredients.

The formulations of the Pharmachemie and Lederle products are presented below:

Component	Pharmachemie per vial	Lederle per vial
Leucovorin Calcium (eq. leucovorin	63.5 mg 50 mg	63.5 mg 50 mg)
NaCl	45 mg	40 mg
NaOH or HCl	pH adjusted to 6.5-8.5	pH adjusted to about 8.1

Each product is reconstituted with Bacteriostatic Water for Injection, USP. Both products are labeled for IV and IM administration.

Comments:

The waiver of an in-vivo bioavailability study may be granted under 21 CFR 320.22 (c)(2) since the parenteral drug has been determined to be safe and effective for at least one indication in a DESI review and the test drug product is similar with respect to active and inactive ingredients to a drug product currently approved in an NDA.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Pharmachemie USA, Inc. demonstrates that its leucovorin calcium lyophilized powder for injection, 50 mg per vial, falls under 21 CFR 320.22 (c)(2) of the Bioequivalence Regulations. The waiver of an in-vivo bioequivalence study for leucovorin calcium lyophilized powder for injection, 50 mg per vial, is granted for the test product. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Lederle's leucovorin calcium lyophilized powder for injection, 50 mg per vial.

2. Therapeutic Equivalence Recommendation:

   The Division of Bioequivalence recommends that the test product be coded AP in the Therapeutic Equivalence List.

2/4/87

Jane F. Kinsel, Ph.D.
Division of Bioequivalence
Review Branch 1

RD INITIALED AJACKSON
FT INITIALED AJACKSON

Concur: _____ Date: 2/6/87
S.V. Dighe, Ph.D.
Director,
Division of Bioequivalence

JKinsel/cc/2-3-87/Wang # 9382e

cc: ANDA # 89-628 original, HFN-230, HFN-200 (Hare), HFN-22 (Hooton), HFN-252 (Jackson, Kinsel), Drug File